Claims

1. Diacylhydrazine derivatives of formula I

A-D-B (I)

wherein

D is a bivalent diacylhydrazine moiety, or a derivative thereof,

A is a unsubstituted or substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L')$_\alpha$, where L is a 5, 6 or 7 membered cyclic structure, selected from the group consisting of aryl, heteroaryl, arylene and heteroarylene, bound directly to D, L' comprises an optionally substituted cyclic moiety having at least 5 members, selected from the group consisting of aryl, heteroaryl, aralkyl, cycloalkyl and heterocyclyl, M is a bond or a bridging group having at least to one atom, α is an integer of from 1-4; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein L' is substituted by at least one substituent selected from the group consisting of $-SO_\beta R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbo atoms, comprising at least one 5-, 6-, or 7-membered cyclic structure, bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein said cyclic structure directly bound to D is selected from the group consisting of aryl, heteroaryl and heterocyclyl,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b, where R_a and R_b are

a) independently hydrogen, a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_γ, where γ is 0-3;

wherein each W is independently selected from the group consisting of -CN, $-CO_2R$, $-C(O)NR^5R^5$, $-C(O)-R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^5$, $-NR^5C(O)OR^5$, $-NR^5C(O)R^5$, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the groups consisting of -CN, $-CO_2R$, $-C(O)NR^5R^5$, $-C(O)-R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^5$, $-NR^5C(O)OR^5$, $-NR^5C(O)R^5$ and halogen up to per-halo;

with each R^5 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, wherein Q is -O-, -S-, $-N(R^5)-$, $-(CH_2)_\beta$, -C(O)-, -CH(OH)-, $-(CH_2)_\beta-$, $-(CH_2)_\beta S-$, $-(CH_2)_\beta N(R^5)-$, $-O(CH_2)_\beta$-CHHal-, $-CHal_2-$, -S-(CH_2).- and $-N(R^5)(CH_2)_\beta-$ where β = 1-3, and Hal is halogen; and Ar is 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Zδ1 wherein δ1 is 0 to 3 and each Z is independently selected from the group consisting-CN, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)-R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-SO_2R^5$, $-SO_3H$, $-NR^5R^5$, $-NR^5C(O)OR^5$, $-NR^5C(O)R^5$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^5$, $-C(O)-R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-SO_2R^5$, $-SO_3H$, $-NR^5R^5$, $-NR^5C(O)OR^5$, $-NR^5C(O)R^5$, and the pharmaceutically acceptable derivatives, salts and solvates thereof.

2. Diacylhydrazine derivative according to claim 1, characterised in that each M independently from one another represents a bond or is a bridging group, selected from the group consisting of $(CR^5R^5)_h$, or $(CHR^5)_h$-Q-$(CHR^5)_i$, wherein

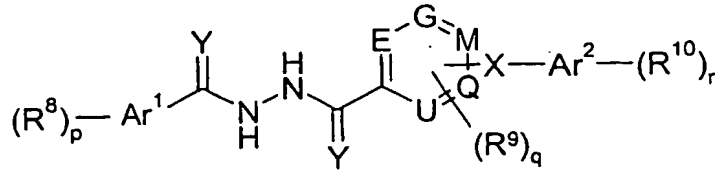
Q is selected from a group consisting of O, S, N-R^5, $CH^{15}H^{16}$, $(CHal_2)_j$, $(O\text{-}CHR^5)_j$, $(CHR^5\text{-}O)_j$, $CR^5{=}CR^5$, $(O\text{-}CHR^5CHR^5)_j$, $(CHR^5CHR^5\text{-}O)_j$, C=O, C=S, $C{=}NR^5$, $CH(OR^5)$, $C(OR^5)(OR^5)$, C(=O)O, OC(=O), OC(=O)O, $C{=}O)N(R^5)C(=O)$, $OC(=O)N(R^5)$, $N(R^5)C(=O)O$, $CH{=}N\text{-}NR^5$, $OC(O)NR^5$, $NR^5C(O)O$, S=O, SO_2, SO_2NR^5 und NR^5SO_2, wherein

R^5 is in each case independently selected from the meanings given above, preferably hydrogen, halogen, alkyl, aryl, aralkyl,

h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and

j is 1, 2, 3, 4, 5 or 6.

3. Diacylhydrazine derivative according to claim 1 or 2, selected from the compounds of formula II,



II

wherein

Ar^1, Ar^2 are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one wo or three hetero atoms, independently selected from N, O und S,

E, G, M, Q and U are selected, independently from one another, from carbon atoms and nitrogen atoms, with the proviso that one or more of E, G, M, Q and U are carbon atoms and that X is bonded to a carbon atom,

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, OA, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^8CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, CH=N-OA, CH_2CH=N-OA, $(CH_2)_nNHOA$, $(CH_2)_nCH$=N-R^{11}, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, CH=$CHCOOR^{13}$, CH=$CHCH_2NR^{11}R^{12}$, CH=$CHCH_2NR^{11}R^{12}$, CH=$CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$,

$(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S,

R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl,

Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

R^{15}, R^{16} are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein

Ar^6 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3,

k, n and m are independently of one another 0, 1, 2, 3, 4, or 5;

X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein

Q is selected from a group consisting of T, $CH^{15}H^{16}$, $(CHal_2)_j$, $(O\text{-}CHR^{18})_j$, $(CHR^{18}\text{-}O)_j$, $CR^{18}=CR^{19}$, $(O\text{-}CHR^{18}CHR^{19})_j$, $CHR^{18}CHR^{19}\text{-}O)_j$, C=O, C=S, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, C(=O)O, OC(=O), OC(=O)O, $C(=)N(R^{15})$, $N(R^{15})C(=O)$, $OC(=O)N(R^{15})$, $N(R^{15})C(=O)O$, CH=N-O, $CH=N\text{-}NR^{15}$, $OC(O)NR^{15}$, $NR^{15}C(O)O$, S=O, SO_2, SO_2NR^{15} und $NR^{15}SO_2$, wherein

T is selected from O, S, N-R^{15},

h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, and

j is 1, 2, 3, 4, 5 or 6,

Y is selected from O/S, NR^{21}, $C(R^{22})\text{-}NO_2$, $C(R^{22})$-CN and $C(CN)_2$, wherein

O/S is selected from O, S,

R^{21} is independently selected from the meanings given for R^{13}, R^{14}, and

R^{22} is independently selected from the meanings given for R^{11}, R^{12},

p, r are independently from one another 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4,

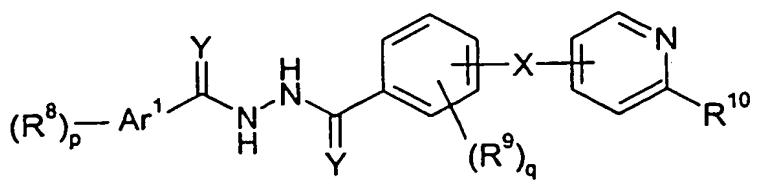
u is 0, 1, 2 or 3,

and

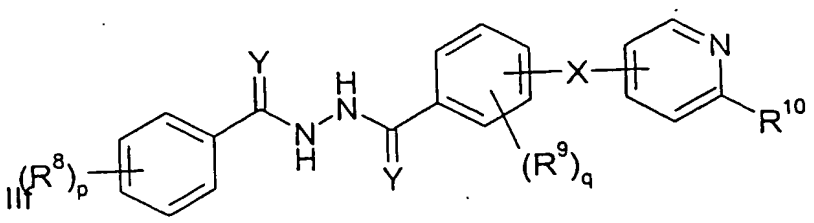
Hal is independently selected from a group consisting of F, Cl, Br and I,

and the pharmaceutically acceptable derivatives, salts and solvates thereof.

4. Diacylhydrazine derivatives according to one of the claims 1 to 3, selected from the compounds of formula IIa, IIb, IIc, IId, IIe, IIf, IIg, IIh, IIi, IIj, IIk, IIL, IIm, IIn, IIo, IIp, IIq, IIr, IIu, IIv, IIw and IIx,

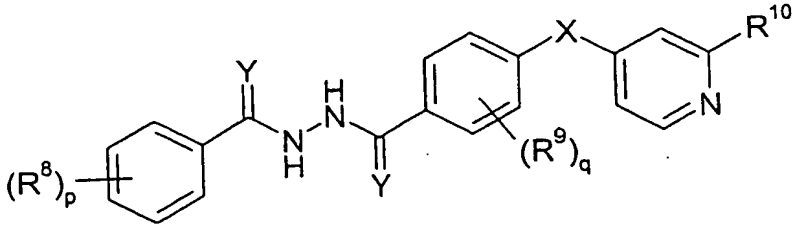


IIa
IId



IIb

IIf



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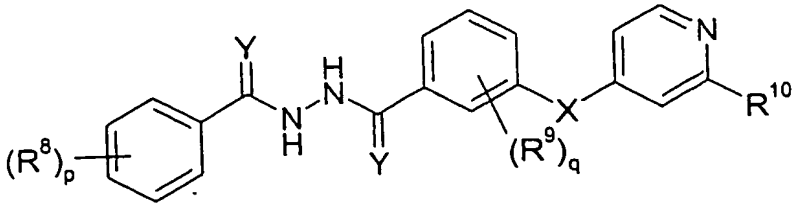

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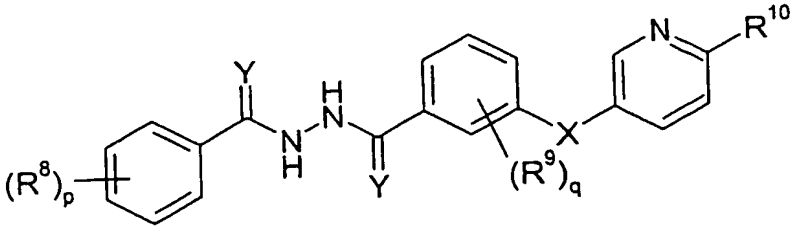

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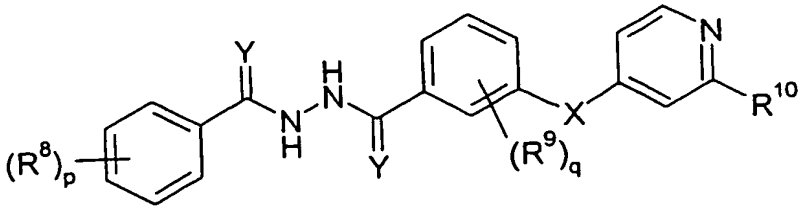

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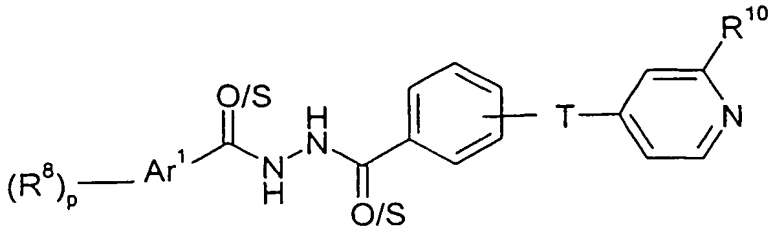

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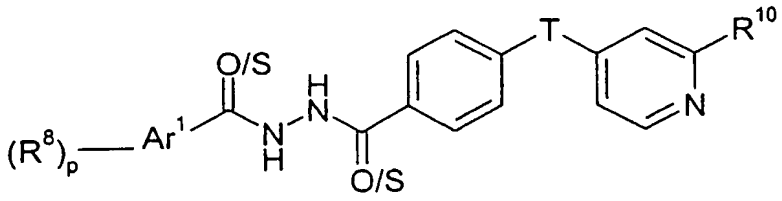

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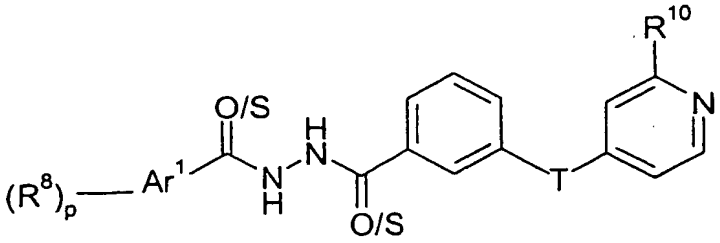

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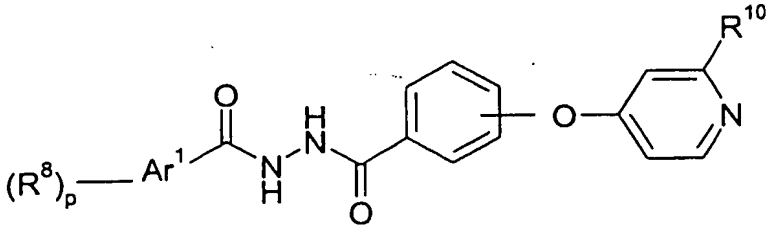

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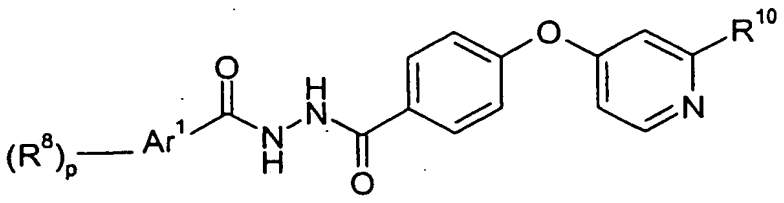

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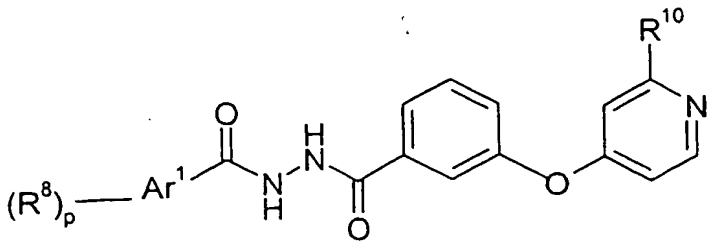

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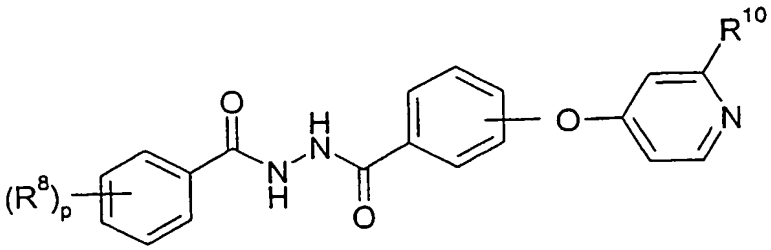

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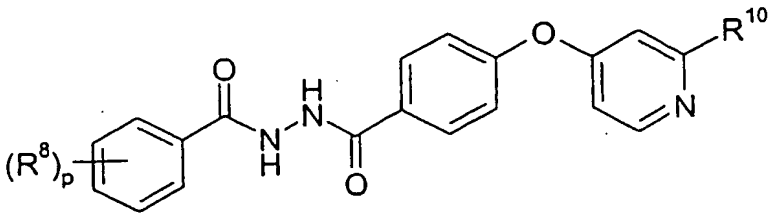

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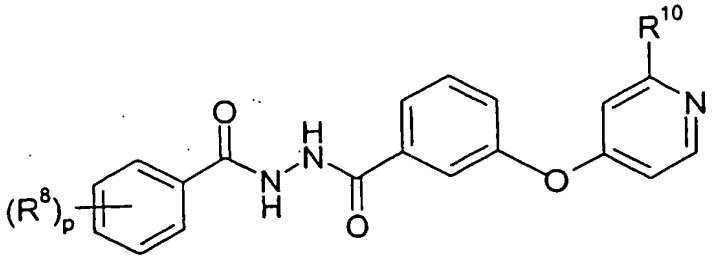

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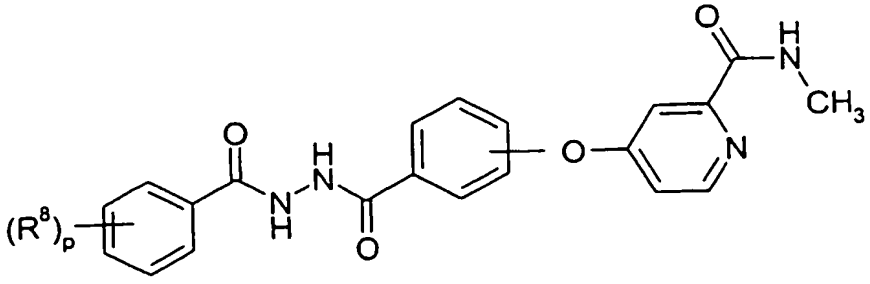

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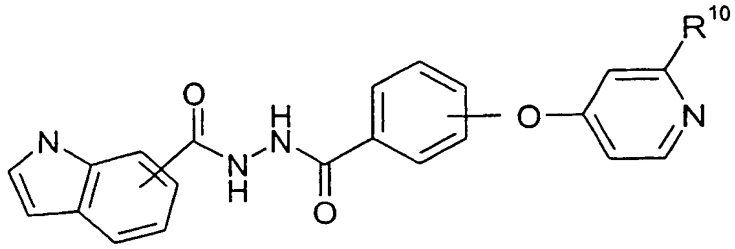

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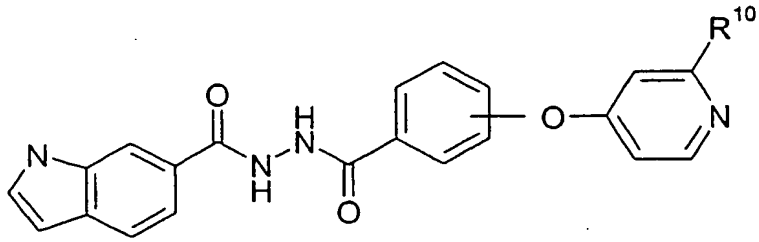

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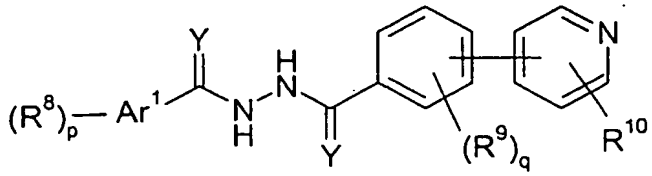

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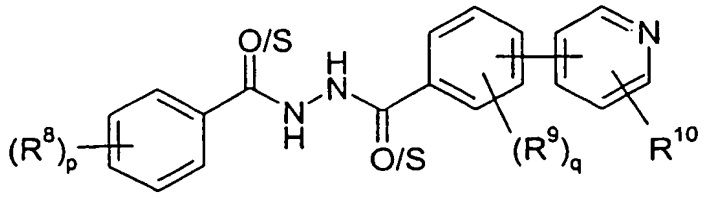

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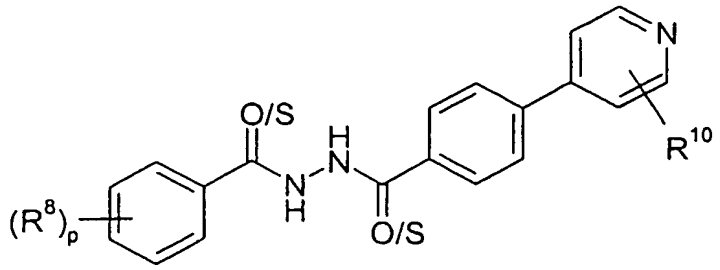

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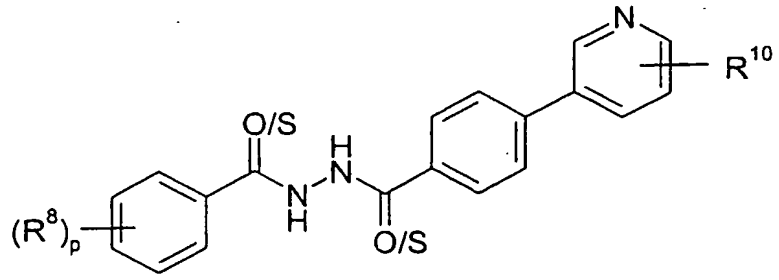

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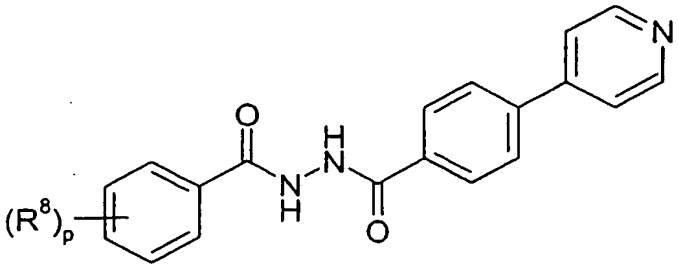

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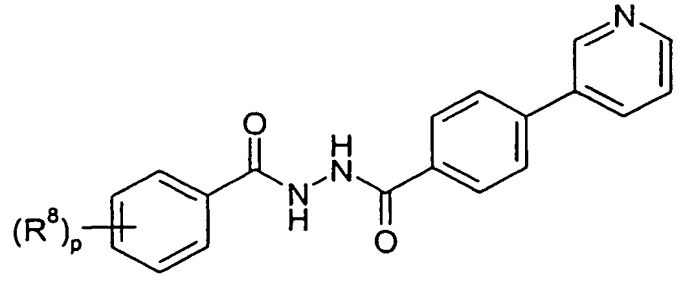


IIx

wherein R^6, R^7, R^8, p, Ar^1, Y, X, R^9 and q are as defined in claim 3, R^{10} is H or as defined in claim 3; and the pharmaceutically acceptable derivatives, salts and solvates thereof.

5. Diacylhydrazine derivative selected from the compounds of formula II as defined in claim 3 or 4, wherein

E, G, M, U and Q	are carbon atoms,
X	is O or a bond,
Y	is O,
Ar^1	is phenyl or indolyl,
Ar^2	is pyridinyl,
R^8	is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, tert.-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, 2-butoxy, tert.-butoxy, Hal, $CHal_3$ or $OCHal_3$,
R^{10}	is H or $CONCH_3$,
p	is 0, 1, 2 or 3,
q	is 0 and
r	is 1

and the pharmaceutically acceptable derivatives, salts and solvates thereof.

6. Diacylhydrazine derivative according to claim 5, wherein

X	is O and
R^{10}	is $CONCH_3$

and the pharmaceutically acceptable derivatives, salts and solvates thereof.

7. Diacylhydrazine derivative according to claim 5, wherein

X	is a bond and
R^{10}	is H

and the pharmaceutically acceptable derivatives, salts and solvates thereof.

8. Diacylhydrazine derivative selected from the compounds of formula II as defined in claim 3 or 4, wherein

E, G, M, U and Q	are carbon atoms,
X	is O, S or NR^{15} and
Y	is O

and the pharmaceutically acceptable derivatives, salts and solvates thereof.

9. Diacylhydrazine derivative according to one of the claims 1, 2 or 3, selected from the compounds (1) to (224) of table 1 and the compounds (225) to (384) of table 2, and the pharmaceutically acceptable derivatives, salts and solvates thereof.

10. Diacylhydrazine derivative according to one of the claims 1 to 9 as a medicament.

11. Diacylhydrazine derivative according to one of the claims 1 to 9 as a kinase inhibitor.

12. Diacylhydrazine derivative according to claim 11, characterized in that the kinases are selected from raf-kinases.

13. Pharmaceutical composition, characterised in that it contains one or more compounds according to one of the claims 1 to 9.

14. Pharmaceutical composition according to claim 13, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 9.

15. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 9 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 9, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.

16. Use of a compound according to one of the claims 1 to 9 as a pharmaceutical.

17. Use of a compound according to one of the claims 1 to 9 in the treatment and/or prophylaxis of disorders.

18. Use of a compound according to one of the claims 1 to 9 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.

19. Use according to claim 17 or 18, characterised in that the disorders are caused, mediated and/or propagated by raf-kinases.

20. Use according to claim 17, 18 or 19, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.

21. Use according to claim 17, 18, 19 or 20, characterised in that the disorder is cancer.

22. Use according to claim 17, 18, 19 or 20, characterised in that the disorder is noncancerous.

23. Use according to claim 22, characterised in that the disorders are selected from the group consisting of psioarsis, arthritis, inflammation, endometriosis, scarring, Helicobacter pylori infection, Influenza A, begnin prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.

24. Use according to one of the claims 17 to 21, characterised in that the disorders are selected from the group consisting of melanoma, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, ovarian cancar, ovary cancer, uterine cancer, prostate cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.

25. Use according to one of the claims 17 to 22, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation, solid tumors,

rheumatic arthritis, diabetic retinopathy, and neurodegenerative diseases.

26. Use according to one of the claims 17 to 20, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.

27. Use of a compound according to one of the claims 1 to 9 as a raf-kinase inhibitor.

28. Use according to claim 27, characterised in that the raf-kinase is selected from the group consisting of A-Raf, B-Raf and c-Raf1.

29. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 9 is administered to a patient in need of such a treatment.

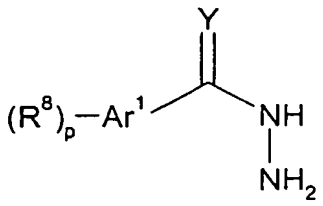
30. Method according to claim 29, characterised in that the one or more compounds according to one of the claims claim 1 to 9 are administered as a pharmaceutical composition according to claim 13 or 14.

31. Method for the treatment and/or prophylaxis of disorders according to claim 30, characterised in that the disorders are as defined in one of the claims 19 to 26.

32. Method for the treatment according to claim 31, characterised in that the disorder is cancerous cell growth mediated by raf-kinase.

33. Method for producing compounds of formula II, characterised in that

a) a compound of formula III

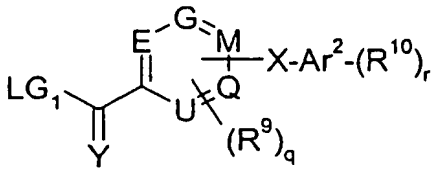


III

wherein Y, R^8, p and Ar^1 are as defined in claim 3,

is reacted

b) with a compound of IV,



IV

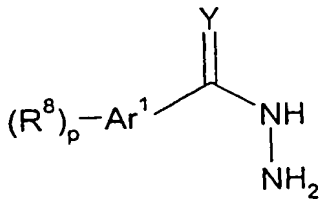
wherein

LG_1 is a leaving group, preferably a leaving group selected from OR^{25}, wherein R^{25} is selected from the group consisting of unsubstituted or substituted aromatic residues, unsubstituted or substituted heteroaromatic residues and $(O)_2S\text{-}R^{26}$, wherein R^{26} is selected from unsubstituted or substituted aromatic residues and unsubstituted or substituted alkyl residues, and wherein E, G, M, Q, U, R^9, q, X, Ar^2, R^{10} and r are as defined in claim 3,

and optionally

c) isolating and/or treating the compound of formula II obtained by said reaction with an acid, to obtain the salt thereof.

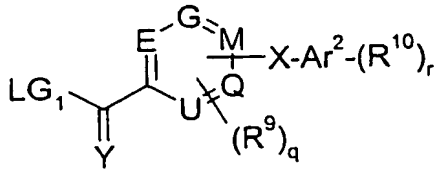
34. Compound of formula III,



III

wherein Y, R^8, p and Ar^1 are as defined in claim 3.

35. Compound of formula IV,



IV

wherein

LG_1 is a leaving group, preferably a leaving group selected from OR^{25}, wherein R^{25} is selected from the group consisting of unsubstituted or substituted aromatic residues, unsubstituted or substituted heteroaromatic residues and $(O)_2S\text{-}R^{26}$, wherein R^{26} is selected from unsubstituted or substituted aromatic residues and unsubstituted or substituted alkyl residues, and wherein E, G, M, Q, U, R^9, q, X, Ar^2, R^{10} and r are as defined in claim 3.